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10/516,618	05/25/2005	Andreas Bergmann	2582.020	7130

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EXAMINER

ROONEY, NORA MAUREEN

ART UNIT	PAPER NUMBER
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1644

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01/29/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/516,618	Applicant(s) BERGMANN, ANDREAS	
	Examiner Nora M. Rooney	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) 10-13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>05/28/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-13 are pending.
2. Applicant's election without traverse of Group I, claims 1-9 and the species of "a method for the diagnosis of sepsis" in claim 1, "IgG in claim 2, "blood fraction" in claim 3, "sandwich assay" in claim 4, "procalitonin" in claim 7, and "Immunochromatographic measuring apparatus" in claim 8 in the reply filed on 10/17/2007 is acknowledged.
3. Claims 10-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/17/2007.
4. Applicant's IDS filed on 05/28/2005 is acknowledged.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
6. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are a contact step and a resolution step: it is unclear how to determine the presence and/or amount of antibodies in the biological fluid. The claimed method cannot be performed by the recited steps because no method of detecting antibodies is recited. There is also no resolution as to how detecting the antibodies relates to sepsis. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination.

B. Claim 1 recites "method for the early diagnosis and diagnosis, for the prognosis and the assessment of the severity and for the therapy accompanying assessment for the course of sepsis and sepsis-like infection and for the estimation of the risk of a sepsis risk patient through the formation of a sepsis." This recitation is extremely confusing and can be read many different ways given that the punctuation and presence of the word "and" does not clarify the phrase.

C. Claim 4 recites "a ligand binding assay of the sandwich type or of the competitive type." It is unclear what Applicant means by this phrase. The Examiner suggests amending the claims to recite "sandwich assay" and "competitive assay."

D. Claim 8 recites "by means of a chip technology measuring apparatus or of a immunochromatographic measuring apparatus." However, the step cannot be carried out by measuring "chip technology" or "immunochromatographic." Therefore, the method must be more particularly claimed and reference to indefinite terms must be corrected.

E. Claim 9 recites "the measuring apparatus" but there is insufficient antecedent basis for the term in base claim 9 as base claim 8 recites two different measuring apparatus. It is unclear which measuring apparatus is being referred to in claim 9.

Correction is required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide reasonable enablement for **a method for the early diagnosis and diagnosis, for the prognosis and the assessment of the severity and for the therapy-accompanying assessment of the course of sepsis and sepsis-like systemic infections**

and for the estimation of the risk of a sepsis risk patient through the formation of a sepsis, characterized in that the **presence and/or amount** of anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) and antibodies cross-reacting therewith in a **biological fluid** of a **patient or sepsis risk patient** are determined and conclusions are drawn from **the presence and/or amount** thereof with regard to **the presence, the expected course, the severity or the success of a therapy of the inflammatory disease or sepsis or with regard to the risk of a sepsis risk patient** of claim 1; characterized in that anti-AG_{M1} and/or anti-G_{M1} (auto) antibodies of the IgG and/or IgA type are determined of claim 2; characterized in that **the biological fluid** is blood, a blood fraction or a secretion of claim 3; characterized in that the determination is carried out with the aid of a **ligand binding assay of the sandwich type or of the competitive type** or of an agglutination assay of claim 4; characterized in that the determination of the antibodies in a blood sample of a sepsis risk patient is carried out after prior in vivo and/or in vitro stimulation of the antibody production of claim 5; characterized in that it is carried out as part of a **multiparameter determination, in which at least one further inflammation or infection parameter is simultaneously determined** and in which a measured result in the form of a set of **at least two measured parameters** is obtained, which result is evaluated for the fine diagnosis of sepsis of claim 6; characterized in that, in addition to the anti-ganglioside autoantibodies, **at least one further parameter which is selected from the group consisting of the proteins procalcitonin, CA 125, CA 19-9, S100B, S100A proteins, LASP-1, soluble cytokeratin fragments, in particular CYFRA 21, TPS and/or soluble cytokeratin-1 fragments (sCY1 F), the peptides inflammin and CHP, peptide prohormones, glycine N- acyltransferase (GNAT), carbamoylphosphate synthetase 1 (CPS 1) and the C-reactive protein (CRP) or**

fragments thereof is determined as part of the **multiparameter determination** of claim 7; characterized in that the **multiparameter determination** is carried out as a simultaneous determination by means of **a chip technology measuring apparatus or of an immunochromatographic measuring apparatus** of claim 8; characterized in that the evaluation of the complex measured result obtained using the measuring apparatus is carried out with the aid of **a computer program**.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses in Figures 1-4 and on pages 25, line 20 to page 31, line 32 that serum from 20 sepsis patients were tested for the presence of antibodies which bind to A G_{M1}; and 89 sepsis patient and 137 normal control patients were tested for the presence of antibodies which bind to G_{M1}. Immunoglobulin IgG and IgA subclasses were determined in the 20 sepsis patients were tested for the presence of antibodies which bind to A G_{M1}. Although Figures 3 and

4 list control patients, the specification only discloses that control patients were measured for the presence of antibodies that bind G_{M1} , not AG_{M1} . The specification discloses on page 31 that because sepsis patients had increased AG_{M1} antibodies of the IgA and IgG subclasses, without having increased AG_{M1} IgM antibodies, then the IgA and IgG antibodies were not formed as a result of the sepsis risk event. In other words, the IgA and IgG antibodies were already present in the patients and contributed to their sepsis or the antibodies were activated in the pre-sensitized immune system. However, the specification establishes no causal link between sepsis and the antibodies.

The specification does not adequately disclose "a method for the early diagnosis and diagnosis, for the prognosis and the assessment of the severity and for the therapy-accompanying assessment of the course of sepsis and sepsis-like systemic infections and for the estimation of the risk of a sepsis risk patient through the formation of a sepsis, characterized in that the presence and/or amount of anti-asialo-GM1 antibodies (anti- AG_{M1} antibodies) and antibodies cross-reacting therewith in a biological fluid of a patient or sepsis risk patient are determined and conclusions are drawn from the presence and/or amount thereof with regard to the presence, the expected course, the severity or the success of a therapy of the inflammatory disease or sepsis or with regard to the risk of a sepsis risk patient" of claim 1. The art teaches that sepsis is not causally linked to the AG_{M1} IgG and IgA antibodies. Badgwell et al. (PTO-892, Reference U) teaches that anti-asialo GM1 antibodies, when injected into mice, deplete their immune systems of NK cells, causing increased (not decreased) lethality due to systemic E. coli infections. (In particular, whole document) The specification discloses that NK cells contribute to lethality in

sepsis patients, but Badgwell et al. teaches otherwise. In fact, Badgwell acknowledges that sepsis patients are shown to have decreased NK cells in their blood, but the reference suggests that decreased NK cells in the blood might have to do with their activation-induced adherence to vascular endothelium, or activation-induced apoptosis. (In particular, page 211, last paragraph). In the same way, Heremans et al. teaches that depletion of NK cells prior to intradermal priming of LPS followed by intravenous LPS challenge leads to a 70% reduction of mortality and cytokine production (In particular, whole document, abstract).

Further, the method of determining the recited antibodies is not a method of "diagnosis" or "early diagnosis" as anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) are present in normal people after 1 month of age because anti-asialo-GM1 antibodies cross-react with LPS (Alaniz et al., Reference W; In particular, page 2149 'Results' section, whole document). Anti-asialo GM1 antibodies are also present in significant numbers in many different disease states. For example: Graves Disease and Hashimoto's Thyroiditis (PTO-892, Reference X; In particular, whole document); Acute Motor Neuropathy (PTO-892, Page 2, Reference U; In particular, abstract); Multiple Sclerosis and Systemic Lupus Erythematosus (PTO-892, Page 2, Reference V; In particular, abstract); Behcets's Disease (PTO-892, Page 2, Reference W; In particular, abstract); and Polyradiculoneuropathy (PTO-892, Page 2, Reference X; In particular, abstract). Because all of these patients have anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) and not sepsis, then anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) is not a diagnostic or early for sepsis. While the presence of anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) might increase risk for sepsis, it does not diagnose it. Further, the specification provides no information how anti-asialo-GM1

antibodies (anti-AG_{M1} antibodies) are related to therapy, prognosis or assessment of severity.

The specification has not adequately disclosed the genus of all biological fluids for use in the claimed invention. The term encompasses urine, tears and saliva, but the specification provides inadequate support for the use of non-blood related tissue in the recited method. A skilled artisan would be required to perform undue experimentation to determine if these and other biological fluids can be used in the claimed invention.

The terms ligand binding assay of the sandwich type or of the competitive type of claim 4; a chip technology measuring apparatus of claim 8; an immunochromatographic measuring apparatus of claim 8; and a computer program of claim 9 are extremely generic and broad, encompassing many products that are not commensurate in scope with the claimed invention and the disclosure set forth in the specification. As such, as skilled artisan would be required to perform undue experimentation to practice the claimed invention commensurate in scope with the claims.

The specification has not adequately disclosed a method for the early diagnosis and diagnosis, for the prognosis and the assessment of the severity and for the therapy-accompanying assessment of the course of sepsis and sepsis-like systemic infections and for the estimation of the risk of a sepsis risk patient through the formation of a sepsis comprising at least one further parameter which is selected from the group consisting of the proteins procalcitonin, CA 125, CA 19-9, S100B, S100A proteins, LASP-1, soluble cytokeratin fragments, in particular CYFRA 21,

TPS and/or soluble cytokeratin-1 fragments (sCY1 F), the peptides inflammin and CHP, peptide prohormones, glycine N- acyltransferase (GNAT), carbamoylphosphate synthetase 1 (CPS 1) and the C-reactive protein (CRP) or fragments thereof is determined as part of the multiparameter determination. The specification has provided no evidence that any of these parameters can be used in the recited diagnostic method, much less by claiming them by name without reference to their specific sequences or specificity. As recited, the claims encompass any protein from any species with the preceeding designations, or any two or more amino acid fragment thereof as is the case with respect to cytokeratin and prohormones in particular. A skilled artisan would be required to perform undue experimentation to practice the invention commensurate in scope with the claims.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of: a method of measuring anti-asialo G_{M1} antibodies in the serum of normal and sepsis patients

Applicant is not in possession of: a method for the early diagnosis and diagnosis, for the prognosis and the assessment of the severity and for the therapy-accompanying assessment of the course of sepsis and sepsis-like systemic infections and for the estimation of the risk of a sepsis risk patient through the formation of a sepsis, characterized in that the presence and/or amount of anti-asialo-GM1 antibodies (anti-AG_{M1} antibodies) and antibodies cross-reacting therewith in a **biological fluid** of a patient or sepsis risk patient are determined and conclusions are drawn from the **presence and/or amount** thereof with regard to the presence, the expected course, the severity or the success of a therapy of the inflammatory disease or sepsis or with regard to the risk of a sepsis risk patient of claim 1; characterized in that anti-AG_{M1} and/or anti-G_{M1} (auto) antibodies of the IgG and/or IgA type are determined of claim 2; characterized in that the **biological fluid** is blood, a blood fraction or a **secretion** of claim 3; characterized in that the determination is carried out with the aid of a **ligand binding assay of the sandwich type or of the competitive type or of an agglutination assay** of claim 4; characterized in that the determination of the antibodies in a blood sample of a sepsis risk patient is carried out after prior in vivo and/or in vitro stimulation of the antibody production of claim 5; characterized in that it is carried out as part of a multiparameter determination, in which **at least one further inflammation or infection parameter** is simultaneously determined and in which a measured result in the form of a **set of at least two measured parameters** is obtained, which result is evaluated for the fine diagnosis of sepsis of claim 6; characterized in that, in addition to the anti-ganglioside autoantibodies, **at least one further parameter** which is selected from the group

consisting of the proteins procalcitonin, CA 125, CA 19-9, S100B, S100A proteins, LASP-1, **soluble cytokeratin fragments**, in particular CYFRA 21, TPS and/or **soluble cytokeratin-1 fragments (sCY1 F)**, the peptides inflammin and CHP, **peptide prohormones**, glycine N-acyltransferase (GNAT), carbamoylphosphate synthetase 1 (CPS 1) and the C-reactive protein (CRP) or **fragments thereof** is determined as part of the **multiparameter determination** of claim 7; characterized in that the **multiparameter determination** is carried out as a simultaneous determination by means of a **chip technology measuring apparatus** or of an **immunochromatographic measuring apparatus** of claim 8; characterized in that the evaluation of the complex measured result obtained using the measuring apparatus is carried out with the aid of a **computer program**.

Applicant has disclosed a method of measuring anti-asialo G_{M1} antibodies in the serum of normal and sepsis patients; therefore, the skilled artisan cannot envision all the contemplated method possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional

characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wirguin et al. (PTO-892, Page 3, Reference U) in view of Weller et al. (PTO-892, Page 3, Reference V) and Kielian et al. (PTO-892, Page 3, Reference W).

Wirguin et al. teaches determining the presence of anti-GM1 and anti-asialo-GM1 antibodies in serum (blood fraction) from patients using ELISA (binding assay of the sandwich type) read by a Biotek EIA reader (immunochromatographic measuring apparatus; computer program) after prior in vivo stimulation of antibody production (In particular, abstract, page 699 'Patients' Sera and Enzyme-linked immunosorbent assay' sections). Wirguin et al. also teaches that anti-asialo GM1 and anti-GM1 antibodies cross react with LPS (a component of gram-negative bacteria).

The claimed invention differs from the prior art by the teaching of "a method for the early diagnosis and diagnosis, for the prognosis and the assessment of the severity and for the therapy-accompanying assessment of the course of sepsis and sepsis-like systemic infections and for the estimation of the risk of a sepsis risk patient through the formation of a sepsis" and "conclusions are drawn from the presence and/or amount thereof with regard to the presence, the expected course, the severity or the success of a therapy of the inflammatory disease or sepsis or with regard to the risk of a sepsis risk patient" of claim 1.

Kielian et al. teaches that Lipopolysaccharide (LPS) is a constituent of the outer cell wall of gram-negative bacteria and is responsible for the overwhelming immune response in the host during sepsis (In particular, 'Introduction on pages 187-188 in particular).

Weller et al. teaches that anti-ganglioside antibodies (including anti GM1) can be used to diagnose inflammatory diseases in a clinical setting by drawing conclusions based on the presence and/or amount of antibody. (In particular, whole document).

It would have been obvious to one of ordinary skill in the art to determine the presence of anti GM1 antibodies in patient samples to assess the severity of sepsis in the patient because Wirguin et al teaches that anti-GM1 and anti-asialo-GM1 antibodies in serum bind to LPS, which Kielian et al teaches is a constituent of the outer cell wall of gram-negative bacteria that is responsible for the overwhelming immune response in the host during sepsis. It would be obvious to determine the amount of "anti-LPS" antibodies that are present in the patient to assess the severity of sepsis, especially since Weller et al. teaches that anti-ganglioside antibodies (including anti GM1) can be used to diagnose inflammatory diseases in a clinical setting.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

12. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wirgin et al. (PTO-892, Page 3, Reference U) in view of Weller et al. (PTO-892, Page 3, Reference V) and Kielian et al. (PTO-892, Page 3, Reference W) as applied to claims 1-5 above and further in view of U.S. Patent 6,756,483.

Wirguin et al., Weller et al. and Kielian et al. have been discussed supra.

The claimed invention differs from the prior art by the recitation of "characterized in that it is carried out as part of a multiparameter determination, in which at least one further inflammation or infection parameter is simultaneously determined and in which a measured result in the form of a set of at least two measured parameters is obtained, which result is evaluated for the fine diagnosis of sepsis" of claim 6; and "characterized in that, in addition to the anti-ganglioside autoantibodies, at least one further parameter which is selected from the group consisting of the proteins procalcitonin, CA 125, CA 19-9, S100B, S100A proteins, LASP-1, soluble cytokeratin fragments, in particular CYFRA 21, TPS and/or soluble cytokeratin-1 fragments (sCY1 F), the peptides inflammin and CHP, peptide prohormones, glycine N- acyltransferase (GNAT), carbamoylphosphate synthetase 1 (CPS 1) and the C-reactive protein (CRP) or fragments thereof is determined as part of the multiparameter determination" of claim 7.

U.S. Patent 6,756,483 teaches using procalcitonin for the diagnosis and therapy of septic diseases. (In particular, abstract, whole document).

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the detection of anti-asialo antibodies to determine the level of antibodies that bind to LPS in a sepsis patient to assess severity of disease with the detection of procalcitonin because procalcitonin levels are taught to be associated with sepsis. It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571)

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272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

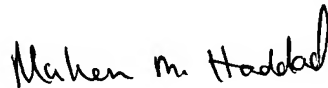
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 20, 2008

Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600



MAHER M. HADDAD
PRIMARY EXAMINER